REMARKS

Claims 1, 3-13, and 28 are pending. Claims 1, 3-6, 8-13, and 28 remain rejected as being anticipated by Fong et al., US 2002/0071832; claims 1, 6, and 7 remain rejected for obviousness over Fong et al., US 2002/0071832, in view of Wong et al., Human Gene Therapy 12:253-265, 2001; and claims 1, 3-6, 8, 9, and 28 remain rejected for obviousness over Kooby et al., FASEB J. 13:1325-1334, 1999, in view of Rodgers and McCall, Brit. J. Surg. 87:1142-1155, 2000. Applicants request reconsideration and withdrawal of these rejections for the reasons set forth below.

First, Applicants point out that the present claims are not drawn to general methods of treating metastases by administration of attenuated oncolytic herpes viruses. Rather, the present claims are more focused, specifying methods in which a tumor is surgically resected and virus is applied to the site of surgical resection, resulting in treatment of metastases that are distal to the site of virus application. This method is not taught or suggested in the prior art.

Rejection under 35 U.S.C. § 102(e)

The anticipation rejection over Fong et al., US 2002/0071832, has been maintained on two grounds. First, the Office Action states that Fong must have envisioned treatment of metastases, as Fong lists a metastasis-specific promoter, mts1, as an example of a promoter that can be used in the methods of Fong. Second, the Office Action states that Fong includes intravenous administration as an example of a mode of administration that can be used in their methods, and cites Henderson, U.S. Patent No. 6,406,861, as teaching "intravenous

administration is desirable for treatment of metastatic disease or non-discrete tumors." These grounds for maintenance of the rejection are addressed as follows.

Regarding Fong's inclusion of the mts1 promoter in a long list of promoters, Applicants disagree that this indicates that Fong envisioned treatment according to the presently claimed invention which, as discussed above, requires surgical resection of a tumor, application of virus to the site of resection, and treatment of a metastasis at a site that is distal to the resection site. This is supported by the accompanying declaration of Dr. Yuman Fong, who is an inventor on both the present application and US 2002/0071832. The declaration states that the passages of US 2002/0071832 cited in this rejection are not a description of a treatment of metastases. In particular, Dr. Fong states US 2002/0071832 mentions the administration of an oncolytic herpes virus to the site of surgical resection of a tumor, and that the purpose of such administration is to kill any residual tumor cells that may exist at the resection site, and not to treat metastases at a site distal to the resection site. Dr. Fong further states that the listings of different promoters (including the mts promoter) and different routes of administration in US 2002/0071832 should not change this interpretation of the method described in US 2002/0071832 involving virus application to a resection site. Rather, Dr. Fong states that the listings of different promoters and routes of administration in US 2002/0071832 should be considered as general listings of exemplary options that could be considered for use in the methods described in US 2002/0071832. Based on this, Applicants submit that it is clear that treatment of metastases according to the present invention is nowhere mentioned in Fong, and Fong's listing of the mts1 promoter does not provide any indication that the claimed method is taught by Fong, expressly or inherently.

Fong lists twenty-four different examples of promoters that can be used in their invention in paragraph 0034, and describes more than twenty routes or modes of administration of virus in paragraph 0036, resulting in nearly 500 possible combinations. Fong does not teach that each and every promoter listed in paragraph 0034 can be used effectively by each and every route listed in paragraph 0036. Rather, it is to be understood that the selection of a promoter and route for use in the method of Fong would depend upon the nature of the disease to be treated. As just one example, in paragraph 0036, Fong mentions as one mode of administration stereotactic injection into a brain tumor. One skilled in the art seeking to treat a brain tumor according to the method of Fong would consider the nature of the tumor in selecting a promoter from the examples listed in 0034, and would understand that not all of the promoters may function in the brain tumor. For example, several of the promoters listed in paragraph 0034 are specific for tumor types that are not brain tumors, and thus those promoters would not be considered as being taught for use in treating brain tumors. If the treated brain tumor had metastasized from a particular type of tumor originating elsewhere in the body, then a promoter specific for tumors from the site of origination may be selected, but not any or all of the promoters listed in paragraph 0034. In view of considerations such as this, as well as the declaration of inventor Dr. Yuman Fong, it is clear that Fong's inclusion of a list of promoters and a list of modes of administration does not mean that Fong teaches each and every combination of these promoter and routes for use in any circumstance.

The route or mode of administration taught by Fong that has been cited with respect to the present claims is inoculation of viruses into resected tumor beds. In consideration of this mode of administration, those of skill in the art would take into account the nature of the cells at

the tumor bed in their selection of a promoter. They would also note Fong's teaching that the purpose of inoculation of virus to the resected tumor bed is to ensure destruction of any tumor cells remaining at the tumor bed. There is no teaching in Fong that would suggest treatment of cells at the tumor bed with a virus including the mts promoter. In fact, there is a teaching to the contrary, as Fong explicitly states that the method is to destroy cells in the tumor bed, and thus the mts promoter would only be considered if it was known that the resected tumor had metastasized from another site (and there is no teaching in Fong of such an example).

In the list of routes and modes of administration in paragraph 0036, Fong includes several which would be applicable to the treatment of metastatic cancer including, e.g., the intravenous route. As noted above, the Examiner cites Henderson in the Office Action for teaching use of the intravenous route for the treatment of metastases. In view of this, Applicants submit that one skilled in the art, in reading Fong, even if considering use of the mts1 promoter in methods involving intravenous administration for the treatment of metastatic disease, would not have considered using the mts promoter in the very different method of treatment by application to a resected tumor bed.

Applicants further submit that the list of promoters in Fong is similar or even identical to those appearing in other patent documents (see, e.g., U.S. Patent No. 6,277,621, column 7, line 57 to column 8, line 40; WO 96/39841, Table 2, pages 24-25), which further supports the position that Fong included the promoters as a general listing, with there certainly not being any specific basis for connecting the use of the mts1 promoter with any particular mode of administration at all, not to mention administration to a resected tumor bed.

Thus, there are nearly 500 possible combinations of promoters and routes/modes of administration possible between paragraphs 0034 and 0036 of Fong, and only a certain subset of these combinations would be selected for use by those skilled in the art, depending upon the circumstance, as discussed above. Use of the mts1 promoter to destroy tumor cells at a resected tumor bed is not a combination that is taught by Fong, and it is not one that one skilled in the art would necessarily select for this purpose. Applicants thus request reconsideration and withdrawal of this ground of rejection over Fong.

Turning now to the second basis for maintaining this rejection, Applicants submit that the facts that Fong mentions use of intravenous administration and that Henderson teaches intravenous administration for treating metastatic disease or non-discrete tumors are not relevant to the present claims. The intravenous administration of Fong and Henderson is carried out so that the administered virus reaches tumor sites, including metastases, by virus being delivered to these sites by the circulatory system. This is in contrast to the presently claimed methods, in which the virus reaches a site of metastasis by administration to a site of surgical resection. Treatment of metastases by administration via the circulatory system, as taught by Fong's mention of intravenous administration and Henderson, is clearly different from the method of the present claims. Virus according to the present invention is administered to the site of a surgical resection, and not to the circulatory system. Prior to the present invention, there was no teaching or expectation in the art that administration of oncolytic virus to a site of surgical resection of a tumor would result in the virus traveling to a distal metastasis from the resection site. Applicants thus request that this ground for maintenance of the rejection for anticipation by Fong be withdrawn.

Applicants further would like to comment upon claims 4, 5, and 28, which specify the treatment of lymphatic metastases. As discussed above, Fong does not teach the treatment of any metastases, let alone lymphatic metastases, and thus certainly does not expressly anticipate these claims. Fong also does not inherently anticipate these claims, as carrying out the method of Fong does not necessarily result in the treatment of such metastases, as not all cancers treated using the method Fong would have them.

Applicants request that the anticipation rejection over Fong be reconsidered and withdrawn in view of the arguments presented above, in addition to the declaration submitted herewith.

Rejections under 35 U.S.C. § 103(a)

Fong in view of Wong

The obviousness rejection over Fong et al., US 2002/0071832, in view of Wong et al., Human Gene Therapy 12:253-265, 2001, has been maintained on the basis that Fong envisioned treatment of metastases by teaching use of the mts1 promoter and intravenous administration, while Wong is cited for teaching oncolytic herpes virus NV1023. As discussed at length above, Fong does not teach or suggest treatment of distal metastases by administration of oncolytic virus to a site of surgical resection of a tumor, as is the subject of the present claims. The mention of the mts1 promoter by Fong certainly does not show that Fong envisioned the presently claimed method, as those of skill in the art would not necessarily have had a basis for selecting this promoter out of the many listed in Fong to use with one of the many listed modes of administration of Fong (to a resected tumor bed). In addition, in describing administration of

virus to tumor beds, Fong states that this is done to destroy any remaining tumor cells. Further, the intravenous administration of Fong results in contact of virus with tumor cells, as delivered via the circulatory system, and thus is distinct from the methods of the present invention, by which virus administered to the site of surgical resection of a tumor is able to treat metastatic cells of a tumor at a distal site. Applicants thus request that this rejection be withdrawn.

Kooby in view of Rodgers and McCall

Applicants now turn to the rejection over Kooby et al., FASEB J. 13:1325-1334, 1999, in view of Rodgers and McCall, Brit. J. Surg. 87:1142-1155, 2000. Applicants respectfully request reconsideration and withdrawal of this rejection for the following reasons.

The Examiner states that Kooby teaches the steps of the claimed method, and that Rodgers was cited to show that certain patients that exhibit metastases in the liver also exhibit metastases in hepatic lymph nodes.

To first address Kooby, Applicants refer to the accompanying declaration of Dr. Yuman Fong, who is an inventor named on the present application and the senior author of the Kooby paper. In the declaration, Dr. Fong states that the method described in the Kooby paper is different from that claimed in the application, as described below. Further, Dr. Fong states that, in reading the Kooby paper, one skilled in the field would not have been led to consider use of the method described in the present application.

In more detail, Dr. Fong explains that, in the Kooby paper, rats were challenged with hepatoma cells administered by injection into exteriorized spleen, from which the cells flowed out of the splenic vein into the portal vein, and from the portal vein into the liver. One week

later, a multi-mutated herpes simplex virus type-1 (G207) was administered to the rats by portal vein infusion. G207-treated livers were found to contain fewer hepatoma-derived nodules than livers from control animals. As the cells and the virus administered according to the method of Kooby entered the liver via the same, known route (the portal vein), Dr. Fong states that it was not unexpected that the virus reached and affected the growth of the administered hepatoma cells in the liver.

Dr. Fong further explains that, in the method of the present application, virus is applied to a site of tumor resection, from where he and his co-inventor found, unexpectedly, the virus travels to distal sites of metastases. Prior to this invention, it was not known that virus applied to the site of a tumor resection travels to such metastases.

Dr. Fong further states that the present method differs from that described in Kooby, as Kooby describes portal vein infusion of virus to the liver to treat cells (or nodules formed therefrom) that had been seeded into the liver via the same, known route. In contrast, in the present invention, a previously known route was not used for virus to reach metastasized tumor cells. Rather, in the present invention, it was found, unexpectedly, that virus administered to a site of tumor resection is able reach another, distal site of metastasis. Dr. Fong then concludes that the Kooby paper does not provide any teaching or suggestion that virus administered to a site of tumor resection could reach a distal site of metastasis of the tumor, as is claimed in the present application. In view of this declaration, Applicants submit that reliance upon Kooby in this rejection should be withdrawn.

Turning now to other points made in the rejection, Applicants note that the Examiner states that the metastatic cancer cells used in the method of Kooby may form tumors in other

parts of the body, and "[b]ecause Kooby et al. teach a method of treating metastases in liver with G207 and teach that metastatic cancer patients who have tumors in their livers often have their tumors resected (Kooby et al., page 1325, 2nd col., 1st parag.), it would have been obvious for an artisan to combine both cancer treatment methods" (page 8 of the Office Action). Applicants respectfully disagree with this basis for the rejection, as combining these two methods does not even result in the claimed method. The claimed method requires administration of virus to the site of tumor resection, for treatment of metastases that are distal to the site of resection. In contrast, if the methods of Kooby are combined, they result in resection and virus administration via portal circulation. These methods are quite clearly distinct.

The Examiner also states in the rejection: "[w]hile the art does not specifically indicate that virus administered to the resected site would treat tumors elsewhere in a patient, the virus would have done so for reasons of inherency" and "...it is reiterated that because Kooby et al. teach the steps of the claimed method, Kooby et al.'s method would inherently treat metastases distal to the site of resection, including metastases in hepatic lymph nodes." Applicants again respectfully disagree.

As noted above, the cited method of Kooby does not teach the steps of the presently claimed method. Administration of virus by Kooby is by portal vein infusion, and not by administration to a resection site, as is required in the present claims. Kooby provides absolutely no basis for consideration of administering virus to a site of surgical resection, or any indication that doing so would result in treatment at a distal site. Inherency also does not apply. As discussed in prior replies in this case, inherency of a method can only be found if the result always occurs, and this is not the case with the method of Kooby, as it may be carried out to

prevent recurrence (not metastasis) and when carried out in this manner, and metastases do not exist, then the result would not occur[1].

In view of the above, Applicants respectfully submit that the obviousness rejection over Kooby and Rodgers and McCall should be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. Please apply any charges not covered or any credits to Deposit Account No. 03-2095.

Respectfully submitted,

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1 M.P.E.P. 2112 states "the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic," (emphasis in original; citations omitted) and that an "allegedly inherent characteristic must necessarily flow from the teachings of the applied prior art" (M.P.E.P. 2112 (IV); citations omitted; emphasis added). Further, M.P.E.P. 2112 states that "the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." This is consistent with the Federal Circuit's discussion of inherency in *Mehl/Biophile International Corp. v. Milgraum*, 192 F.3d 1362, 52 U.S.P.Q.2d 1303 (Fed. Cir. 1999). In this case, the Court states that "[u]nder the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates" and that "occasional results are not inherent."